UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,732	12/26/2006	Claudia Magagnoli	PP021455.0004 (2300-21455	5728

27476 7590 02/24/2010

NOVARTIS VACCINES AND DIAGNOSTICS INC.
INTELLECTUAL PROPERTY- X100B
P.O. BOX 8097
Emeryville, CA 94662-8097

EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
02/24/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/576,732	**Applicant(s)** MAGAGNOLI ET AL.	
	Examiner Jennifer E. Graser	**Art Unit** 1645	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 18 February 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *none*.
   Claim(s) objected to: *none*.
   Claim(s) rejected: *1,4,5,9,10,12,14 and 43-45*.
   Claim(s) withdrawn from consideration: *11,15,17,18,23,25,27-42,47 and 48*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Jennifer E. Graser/
Primary Examiner, Art Unit 1645

Continuation of 5. Applicant's reply has overcome the following rejection(s): rejection of claims 1, 2, 6-8, 12-14 and 43-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Pizza et al (US-A-2002/0044939) and rejection of claims 1, 2, 6-8, 12-14, and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Pronk et al (J.Biochem.Chem. 1985.260(25): 13580-13584); .

Continuation of 11. does NOT place the application in condition for allowance because: the pending claims remain rejected under 35 USC 112, first paragraph rejection. 2.
Claims 1, 4, 5, 9, 10, 12, 14, and 43-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "a composition comprising an isolated LTK63 protein and arginine phosphate and CHAPS", does not reasonably provide enablement for the recited claims as set forth in the Final Rejection mailed 12/23/09.

Applicants have argued that it would be routine for the skilled artisan to provide compositions comprising other LT or CT toxin in combination with a charged amino acid and a zwitterionic detergent inasmuch as LT holotoxins were, at the time of filing, known to be similar in structure and function. See, e.g., pages 13-14, noting the well-characterized nature of CT and LT endotoxins and that these two proteins are "structurally, functionally and immunologically" similar, including in that LT and CT are immunologically cross-reactive. They argue that the skilled artisan would know that any LT or CT protein could be used in the claimed compositions and that the skilled artisan, armed with the teachings of the specification and in view of the state of art, would know charged amino acids other than those exemplified (Arg) can be used to stabilize LT or CT proteins. Pages 18-28, including Table 8 on page 21 of the as-filed specification1 are specifically cited. It is also argued that it would be routine in light of the as-filed specification to use any zwitterionic detergent to stabilize the LT or CT protein, as such agents were well known in the art and described in the specification (see, e.g., paragraphs [0107]-[0113] at page 22-page 23).

These arguments have been fully and carefully considered but are not deemed persuasive. The specification has demonstrated that the particular agents, arginine phosphated and CHAPS work to greatly stabilize the LTK63 protein. The specification has not demonstrated that said agents would be effective in stabilizing any other bARE class protein. The instant specification fails to enable any other composition with an effective stabilizing agent. The prior art (see Wang, W. International J. Pharmaceutics, 199, 185: 129-188; e.g., 'Conclusions') teaches that the stabilization of polypeptides in pharmaceutical areas is unpredictable and that trials and errors play major roles in finding an effective combination. The art is highly unpredictable. The instant claims encompass the use of any bARE protein with any stabilizing agent, any charged amino acid or any uncharged amino acid. The specification does not encompass the scope of these claims. It is unclear what structure is encompassed by an 'analog' of any charged or uncharged amino acid. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention."

The specification teaches that there was a long felt need in the art for a suitable means to stabilize the bARE class proteins. There is established unpredictability among agents. The specification at page 21 teaches that there are some confilicting reports on the benefits of an amorphous excipient in terms of stabilization and that some studies have shown that the addition of amorphous exoipients to protein solutions can actually destabilise a protein through interactions between the excipient and the protein (see for example, Pike et a@ Biopharm 1990 3:2629 and WO01/41800). Without wishing to be bound by theory, zwittergents, such as CHAPS, are advantageous because they are less denaturing than the Zwittergent® 3-X series, possibly owing to their rind steroid ring structure. Thus, zwittergents, such as CHAPS, may enhance the stable association of the A and B subunits. The specification at the bottom of page 24 teaches that the identification of charged Arginine as a stabilizing agent is unexpected.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidancepresented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7)the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to the ability of other amino acids, proteins and zwitteronic detergents and their ability to provide a stabilized protein 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). With regard to (4) the nature of the invention and (5) the state of the prior art, these have been discussed in the previous Office Actions.